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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/930,480	01/21/1998	LAURENT BRACCO	ST95021-US	3058

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EXAMINER
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ART UNIT	PAPER NUMBER
1636	37

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/930,480	BRACCO ET AL.	
	Examin r	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 1999 and 19 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-108* is/are pending in the application.

4a) Of the above claim(s) *59,60,64,66-71,73,78,81-91,94,98-104 and 108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,61-63,65,72,74-77,79,80,92,93,95-97 and 105-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *19 February 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, species antibody fragment, SEQ ID NO:5, SEQ ID NO:7, TetR DNA binding domain, TATA box, and protein having transcriptional transactivating activity, claims 58, 61-63, 65, 72, 74-77, 79-80, 92-93, 95-97, and 105-107 in Paper No. 13, filed 9/23/99 is acknowledged. The traversal is on the ground(s) that the species of the invention are drawn to a single inventive concept and that claims 58-108 are drawn to a single inventive concept and share a special technical feature. It is also argued that few inventions are in closer relationship than a protein and the nucleic acid encoding the protein and that the two exhibit corresponding technical features. It is also argued that examination of the entire application can be made without serious burden and that it is not even averred by the examiner that the two groups are classified separately. This is not found persuasive because under PCT Rule 13.2 (which is the proper basis for restriction because the instant application is a 371 application), unity of invention exists only when the shared same or corresponding technical feature is a contribution over the art. As shown by the corresponding international

preliminary examination report, the bispecific molecule as claimed does not have a special technical feature because there is prior art teaching it, which is also shown by the rejections under 35 USC 102 and 35 USC 103 set forth below. Therefore, in the absence of a special technical feature, the groups lack unity of invention and it is proper to restrict them in the instant corresponding U.S. application. With regard to the argument concerning separate classification and burden, this argument is not persuasive because those elements of a proper restriction apply to U.S. cases that are not 371 cases. 371 cases use lack of unity rules under PCT for the basis of restriction, which basis does not include arguments concerning classification and search burden. That is why these elements were not addressed in the restriction: they do not apply.

The requirement is still deemed proper and is therefore made FINAL.

Claims 59-60, 64, 66-71, 73, 78, 81-91, 94, 98-104, and 108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Drawings

The corrected or substitute drawings were received on 2/19/03. These drawings are acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58, 61-63, 65, 72, 74-77, 79-80, 92-93, 95-97, and 105-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of "bending domain" in claim 58 renders the claims vague and indefinite because a review of the specification did not identify a basis for this term even though it is a term of the transcription factor art, and thus it appears that "binding" was intended instead of "bending". Amending the claim to recite "binding" instead of "bending" would be remedial.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof

> by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 58, 61-63, 65, 92-93, 95-97, and 105-107 are rejected under 35 U.S.C. 102(e) as being anticipated by Bujard et al (U.S. Patent No. 5,650,298).

Bujard et al teach a system for regulating expression of eukaryotic genes using components of the Tet repressor/operator/inducer system of prokaryotes. In the system of the invention, transcription of a nucleotide sequence operably linked to at least one tet operator sequence is stimulated by a tetracycline (Tc)-controllable transcriptional activator fusion protein (referred to herein as tTA). The tTA is comprised of two polypeptides. The first polypeptide is a (full length) Tet repressor (TetR; e.g., a Tn10-derived tetR),

which binds to tet operator sequences in the absence but not the presence of Tc. The second polypeptide directly or indirectly activates transcription in eukaryotic cells (columns 1-2). The second polypeptide can be a domain (e.g. dimerization domain) which recruits a transcriptional activator (e.g. an endogenous transcriptional activator) to interact with the tTA fusion protein by protein-protein interaction (e.g., a non-covalent interaction) (column 2). This reads on the claimed bispecific chimeric molecule because the fusion protein of TetR with a second polypeptide which indirectly activates transcription by recruiting an endogenous transcriptional activator is done through binding and the endogenous transcriptional activator is characteristic of at least a physiological state (the activation of the gene(s) regulated by that endogenous transcriptional activator) and the absence of that endogenous transcriptional activator means that the genes normally regulated by that activator are not and thus that lack of activation is a physiopathological situation.

Bujard et al also teach a system comprising the tTA and a Tet operator sequence (the regulatory sequence the tTA binds to, which comprises SEQ ID NO:1), a minimal promoter comprising at least a portion of the CMV IE promoter or Tk promoter (both of which comprises a TATA box) and a gene, all operably linked

reading on an expression cassette, wherein binding of the tTA activates transcription (columns 12-14 and columns 62-63).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 58, 61-63, 65, 72, 74, 79, 92-93, 95-97, and 105-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al (U.S. Patent No. 5,650,298) in view of Hupp et al (Applicant reference PC) and Mezes et al (U.S. Patent No. 5,892,020).

Bujard et al teach a system for regulating expression of eukaryotic genes using components of the Tet repressor/operator/inducer system of prokaryotes. In the system of the invention, transcription of a nucleotide sequence operably linked to at least one tet operator sequence is stimulated by a tetracycline (Tc)-controllable transcriptional activator fusion protein (referred to herein as tTA). The tTA is comprised of two polypeptides. The first polypeptide is a (full length) Tet repressor (TetR; e.g., a Tn10-derived tetR), which binds to tet operator sequences in the absence but not the presence of Tc. The second polypeptide directly or indirectly activates transcription in eukaryotic cells (columns 1-2). The second polypeptide can be a domain (e.g. dimerization domain) which recruits a transcriptional activator (e.g. an endogenous transcriptional activator) to interact with the tTA fusion protein by protein-protein interaction (e.g., a non-covalent interaction) (column 2). This reads on the claimed bispecific chimeric molecule because the fusion protein of TetR with a

second polypeptide which indirectly activates transcription by recruiting an endogenous transcriptional activator is done through binding and the endogenous transcriptional activator is characteristic of at least a physiological state (the activation of the gene(s) regulated by that endogenous transcriptional activator) and the absence of that endogenous transcriptional activator means that the genes normally regulated by that activator are not and thus that lack of activation is a physiopathological situation.

Bujard et al also teach a system comprising the tTA and a Tet operator sequence (the regulatory sequence the tTA binds to, which comprises SEQ ID NO:1), a minimal promoter comprising at least a portion of the CMV IE promoter or Tk promoter (both of which comprises a TATA box) and a gene, all operably linked reading on an expression cassette, wherein binding of the tTA activates transcription (columns 12-14 and columns 62-63).

Bujard et al do not specifically teach the domain in tTA which binds to a transactivator as being an antibody, specifically a single chain antibody, or the DNA-binding domain is at the C-terminus and the transactivator-binding domain is at the N-terminus.

Hupp et al teach monoclonal antibody pAb421, which binds p53 and activates p53 (abstract; Results section). p53 is

taught as being a cellular protein that is involved in sequence-specific binding/transcriptional activation in cancer (page 875).

Mezes et al teach construction of single-chain antibodies from multi-chain antibodies, which allow for the construction of an antibody fragment which has the specificity and avidity of a whole antibody but are smaller in size, and can be easily expressed by expression vectors (columns 1-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the tTA system taught by Bujard et al by using single chain monoclonal antibody as the domain that binds to the transactivator, as taught by Mezes et al, using as a basis for the antibody pAb421, which Hupp et al teaches binds to p53, a transactivator protein involved in cancer, because Bujard et al teaches that it is within the ordinary skill in the art to use any domain in tTA which indirectly interacts with a transcriptional activator by binding, Mezes et al teach that it is within the ordinary skill in the art to construct single-chain antibodies from multi-chain antibodies which has the specificity and avidity of a whole antibody and which can be expressed in expression vectors, and Hupp et al teaches a specific antibody that binds to p53 and

endogenous transactivator involved in cancer, which binding activates p53.

One would have been motivated to do so for the expected benefit of making a tTA that activates the same genes as p53, which is involved in cancer, as taught by the combined teachings of the cited references. Based upon the teachings of the cited the references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 58, 61-63, 65, 75-77, 92-93, 95-97, and 105-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al (U.S. Patent No. 5,650,298) in view of Whitlow et al (U.S. Patent No. 5,990,275).

The teachings of Bujard et al are set forth above and applied as before. Bujard et al also teach that the linkage between the components of the fusion protein can be done using any means that preserves the function of each polypeptide (column 11).

Bujard et al do not specifically teach use of an arm consisting of from about 5 to 20 amino acids, such as SEQ ID

NO:5 in linking the DNA binding domain and the second polypeptide.

Whitlow et al teach the use of peptide linkers (18-50 amino acids in length) for connecting polypeptide constituents together into a fusion polypeptide (abstract). The purpose of the linker is to provide greater stability and decreased susceptibility to aggregation (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the peptide linkers taught by Whitlow et al, or any other linkers known in the art, such as SEQ ID NO:5, in making the fusion tTA protein taught by Bujard et al because Bujard et al teach making fusion proteins between a DNA binding domain and a polypeptide that binds with a transactivator, linking them using any means taught that preserves the function of each polypeptide, and Whitlow et al teach the use of peptide linkers of 18 to 50 amino acids for connecting polypeptide constituents together into a fusion polypeptide.

One would have been motivated to do so for the expected benefit of providing greater stability and decreasing susceptibility to aggregation as taught by Whitlow et al for the tTA taught by Bujard et al. Based upon the teachings of the cited the references, the high skill of one of ordinary skill in

the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be

responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

May 5, 2003